SELF FORMING, THERMODYNAMICALLY STABLE LIPOSOMES AND THEIR APPLICATIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of and claims priority based on co-pending U.S. patent application Ser. No. 10/262,284 entitled "Self Forming, Thermodynamically Stable Liposomes and Their Applications", filed on Sep. 30, 2002 now U.S. Pat. No. 6,958,160, in the name of the same inventors and commonly owned herewith; which is a continuation of and in turn claims priority based on U.S. Pat. No. 6,610,322, which issued from U.S. patent application Ser. No. 09/745,292, entitled "Self Forming, Thermodynamically Stable Liposomes and Their Applications", filed on Dec. 20, 2000, in the name,of the same inventors and commonly owned herewith.

FIELD OF THE INVENTION

The present invention relates to liposomes. More particularly, the present invention relates to liposomes which form spontaneously upon mixing of lipids and an aqueous solution, and applications thereof.

BACKGROUND OF THE INVENTION

Liposomes are self-closed colloidal particles in which membranes composed of one or more lipid bilayer(s) encapsulate a fraction of the aqueous solution in which they are suspended. The surfaces of bilayers are hydrophilic while the interior of bilayers, which contain hydrocarbon chains, are hydrophobic. Because of the different microenvironments in their structure, liposomes can encapsulate hydrophilic molecules, bind molecules on the bilayer surfaces or dissolve hydrophobic molecules into the middle of the bilayer. Their ability to incorporate many types of molecules has resulted in applications for drug delivery, diagnostics, cosmetics, cosmeceuticals and nutraceuticals.

Liposomes are manufactured by several different methods. Typically, the process begins when a lipid or combination of lipids are dissolved in an organic solvent. Upon removal of organic solvents and hydration, large multilamellar vesicles (MLVs) are formed. For some applications, small unilamellar vesicles (SUVs) may be desired. SUVs can be produced from MLVs by several techniques including sonication, extrusion through membranes with well-defined pores, French press extrusion and homogenization.

Problems associated with liposomes include colloidal instability, difficulty in scale-up sterilization, and variability between batches in manufacturing. Liposome preparation and manufacturing typically involves removal of organic solvents followed by extrusion or homogenization. These processes may expose liposomal components to extreme conditions such as elevated pressures, elevated temperatures and high shear conditions which can degrade lipids and other molecules incorporated into the liposomes.

Liposome preparations are often characterized by very heterogeneous distributions of sizes and number of bilayers. Conditions optimized on a small scale normally do not scale up well and preparation of large-scale batches is cumbersome and labor intensive.

Another issue associated with liposomes for medical uses is sterilization. Among heat sterilization, ethanol oxide exposure, gamma irradiation and sterile filtration, only the last technique is suitable for liposomes and then only for liposomes smaller than about 100 nanometers (nm). Filtration of liposomes poses many difficulties.

Another problem for liposome applications is colloidal stability. Liposomes in suspension can aggregate and fuse upon storage, heating and addition of various additives. Because of these stability problems, liposomes are often lyophilized. Lyophilization is costly and time consuming. Upon reconstitution, size distributions often increase and encapsulated materials may leak out from the liposomes.

It is therefore desirable to develop new methods and materials which address these problems with current liposome formulations.

BRIEF DESCRIPTION OF THE INVENTION

A liposome suspension forms spontaneously upon adding a lipid composition to an aqueous solution. The lipid composition comprises a single lipid or a mixture of lipids that have appropriate packing parameters, that includes polyethyleneglycol, and that has a melting temperature which allows it to be in liquid form when mixed with the aqueous solution. Such liposome suspensions are useful for a variety of purposes, including the delivery of therapeutic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated into and constitute a part of this specification, illustrate one or more embodiments of the present invention and, together with the detailed description, serve to explain the principles and implementations of the invention.

In the drawings:

FIG. **1** is a diagram depicting the cross-section of a liposome made of lipid molecules.

FIG. **2** is a space-filling diagram of a lipid molecule having a polar head group and nonpolar hydrocarbon chains.

FIG. **3** is a diagram depicting a cross-section of a micelle made of lipid molecules.

FIG. **4** is a diagram depicting a cross-section of a structure made of lipid molecules with large tails relative to the head groups.

FIG. **5** is a diagram showing the molecular structure of PEG-12 Glyceryl Dioleate or Hetoxamate GDO-12.

DETAILED DESCRIPTION

Embodiments of the present invention are described herein in the context of a self-forming, thermodynamically stable liposomes and their applications. Those of ordinary skill in the art will realize that the following detailed description of the present invention is illustrative only and is not intended to be in any way limiting. Other embodiments of the present invention will readily suggest themselves to such skilled persons having the benefit of this disclosure. Reference will now be made in detail to implementations of the present invention as illustrated in the accompanying drawings. The same reference indicators will be used throughout the drawings and the following detailed description to refer to the same or like parts.

In the interest of clarity, not all of the routine features of the implementations described herein are shown and described. It will, of course, be appreciated that in the development of any such actual implementation, numerous implementation-specific decisions must be made in order to achieve the developer's specific goals, such as compliance with application- and business-related constraints, and that